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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/685,319	10/14/2003	Laurence A. Nafie	35203-94789	5029

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EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	**PAPER NUMBER**
1743	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

Office Action Summary	**Application No.**	**Applicant(s)**	
	10/685,319	NAFIE ET AL.	
	Examiner	**Art Unit**	
	Arlen Soderquist	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-14* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-29-04 and 5-1-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed to a method, but do not contain any method steps. These claims need to be consistent with the type of claim identified in the preamble. For examination purposes they will be treated consistent with the means they describe rather than as method claims.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Shah. In the paper Shah discusses spectroscopic methods for determining enantiomeric purity and absolute configuration in chiral pharmaceutical molecules. Analytical support, such as methods development, along with identification and characterization of intermediates and impurities, are critical in the development of a chemical process. The preparation of a drug substance requires the development of analytical methods for monitoring reactions and identifying impurities. Methods development for a chiral drug molecules is more difficult as the method must be capable of monitoring the overall reaction as well as possible racemization of starting materials and products. Chiral methods are often required to monitor the reaction steps of a synthesis, however, the development of enantiomeric purity methods are time-consuming and expensive. The use of chiroptical detectors, such as CD (CD), optical rotation (OR) and vibrational CD (VCD), can help to reduce or eliminate the need to develop chiral monitoring methods and also to predict absolute configuration. Recently, VCD has shown remarkable success with the latter and currently holds the most promise as a general, direct method that can be used as an alternative to X-ray crystallography. Each of the mentioned techniques can help analytical chemists to reduce the time associated with traditional enantiomeric purity methods development and to determine absolute configuration. The review discussed the scope and limitations of these techniques for the rapid and routine determination of both enantiomeric excess and absolute configuration. Page 770 teaches that a continuous flow sampling accessory was made for simultaneous determination of the composition and percentage enantiomeric excess. The last

full paragraph of page 770, teaches that the VCD spectrum is proportional to the product concentration and percentage enantiomeric excess, while the IR spectrum is proportional to the concentration. Thus by dividing the observed VCD by the concentration obtained from the IR spectrum to obtain a VCD spectrum that is corrected to a constant value of concentration. The paragraph bridging pages 770-771 teaches that the apparent concentration of the components can be obtained from the VCD by chemometric methods and this concentration can be divided by the IR concentration to obtain the percentage enantiomeric excess without the need of separating the components. The paragraph also teaches that application of this methodology to real-time analysis of slowly evolving chemical reactions of chiral molecules of varying percentages is straightforward.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-4, 9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah as applied to claims 7-8 above, and further in view of Sivakesava and Chickos, Cianciosi (1990 and 1991, hereinafter called Cianciosi '90 and Cianciosi '91, respectively), Freedman or Setnicka. Shah does not teach actual examples of applying the method to a time developing reaction or the use of NIR.

In the paper Sivakesava teaches that bioprocess optimization is often limited by its inability to measure biomass, nutrients and product concentrations in a time frame that allows process adjustments. Infrared spectroscopic techniques can potentially be used to measure each of these components within about 3 minutes of sampling, of an unprocessed whole broth sample. In the present study, the use of Fourier transform mid infrared (FT-MIR), near infrared red (NIR), and Fourier transform (FT)-Raman spectroscopic techniques for at-line (rapid off-line) monitoring of biomass, glucose, and lactic acid in a lactic acid fermentation by Lactobacillus casei was investigated. Suitable spectral wavenumber regions were selected for principal least square (PLS) regression and principal component regression (PCR) and calibration models were developed. The standard error of calibration for the PLS-1st derivative calibration models for glucose, lactic acid, and optical cell density were 2.5, 0.7 g/l, and 0.23, respectively. Prediction errors were high for NIR and FT-Raman methods. Results indicated that FT-MIR spectroscopy could be used for rapid detection of glucose, lactic acid, and optical cell density during lactic acid fermentation.

In the paper Chickos discusses the thermolysis of (1R,2R)-1,2-dideuteriocyclobutane. An application of vibrational circular dichroism to kinetic analysis. The relative rates of geometric isomerization to racemization have been studied for the compound by using a combination of IR and vibrational CD (VCD) spectroscopies, respectively. The results are interpreted with a kinetic and mechanistic scheme which parallels that used by another group on a similar study of chiral cyclopropane-d2 thermolysis. Relative rates of isomerization to stereomutation of 1.5 ±0.4 were obtained which are consistent with a mechanism best described by random methylene rotation in tetramethylene-d2. This is the first application of VCD to kinetic analysis, and the advantages of IR techniques over the more usually employed UV spectroscopies to this type of basic mechanistic problem are illustrated. The method uses several time related spectra to make the calculations.

In the paper Cianciosi '90 measured the racemization and geometrical isomerization of a compound using infrared spectroscopy and vibrational circular dichroism at different times to monitor the reaction.

In the paper Cianciosi '91 measured the racemization and geometrical isomerization of (2S,3S)-cyclopropane-1-13C- 1,2,3-d3 at 407 °C. Both enantiomers of the compound were prepared, and the kinetics of the gas-phase thermal stereomutation reactions were followed by FTIR and tunable diode laser spectroscopy, and by vibrational CD spectroscopy.

In the paper Freedman discusses the kinetics of thermal racemization of (2S,3S)-1-13C-1,2,3-d3-cyclopropane followed by vibrational circular dichroism spectroscopy.

In the paper Setnicka describes a novel approach to study the sol-gel phase transition of a brucine-porphyrin based gelator, which uses vibrational CD (VCD) spectroscopy. The gelation process leading to highly ordered chiral supramolecular assemblies was investigated in various solvents at the different temperatures and concentrations. The VCD spectra sensitively reveal the specific parts of the molecule whose configuration is influenced by a sol-gel phase transition and chiral supramolecular aggregation and therefore indicate the parts of the molecule responsible for the chiral self-assembly formation. Temperature stability of the organogel studied is discussed on the basis of the VCD and IR absorption spectra. The SEM was used to visualize the structure of brucine-porphyrin conjugate in the gel phase.

It would have been obvious to one of ordinary skill in the art to optimize a bioreaction as taught by Sivakesava or a reaction as taught by Chickos, Cianciosi (1990 and 1991), Freedman or Setnicka by following the reaction with the methods of Shah using radiation from the different regions taught by Sivakesava because of the ability to follow a reaction and optimize the process conditions or derive kinetic information from the data as taught by Sivakesava, Chickos, Cianciosi '90, Cianciosi '91, Freedman or Setnicka.

6. Claims 5-6 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah in view of Sivakesava and Chickos, Cianciosi '90, Cianciosi '91, Freedman or Setnicka as applied to claims 1-2 and 9 above, and further in view of Edelmann. Shah does not teach the use of optical fibers to carry the light to and from the sample undergoing reaction.

In the paper Edelmann teaches functional group-specific detection in high-performance liquid chromatography using mid-infrared quantum cascade lasers. A distributed feedback quantum cascade laser was applied for the first time as a powerful light source for mid-infrared (MIR) detection in liquid chromatography. Fructose and glucose in red wine were separated with an isocratic HPLC system, which was connected to a custom-made flow cell. This flow cell was constructed of two diamond windows with adjustable spacing and two hollow wave-guides (optical fibers, see figure 1) for guiding the incoming and outgoing light. The HPLC column based on an ion-exchange resin with calcium (II) counter ion was run at 80°C with 0.04% formic acid as the mobile phase. Under these conditions the carbohydrates could not be completely separated from the organic acids also present in wine. However, the emission of the laser at 1067 cm-1 matches the absorption maximum of fructose and glucose, whereas the organic acids do not absorb appreciably at this wavenumber. Thus group-specific detection could be achieved. Additionally, the optical path length could be increased from 25 to 125 µm, which is very promising in gaining enhanced sensitivity compared to Fourier transform IR detection.

It would have been obvious to one of ordinary skill in the art to incorporate the optical fibers of Edelmann into the device and method of Shah as a radiation guide into and out of the flow cell because of the recognized advantages and properties of waveguides.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571) 272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Arlen Soderquist

Arlen Soderquist
Primary Examiner
Art Unit 1743